REMARKS

Reconsideration is requested.

Claims 94, 102, 103, 105-108, 117-119 and 126, have been canceled, without prejudice.

Claims 87-93, 101, 104, 109-116 and 120-125 are pending.

No new matter has been added.

The applicants acknowledge, with appreciation, the Examiner's indication that the claims are patentable over the art of record.

The claims have been amended to obviate the Section 112, second paragraph, rejection of claims 90, 94 and 101-103. Specifically, claims 90 and 101 have been amended to remove the objected-to recitation; and claims 94, 102 and 103 have been canceled, without prejudice. Withdrawal of the Section 112, second paragraph, rejection of claims 90, 94 and 101-103, is requested.

The Section 112, first paragraph, rejection of claims 87-126 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner's acknowledgement that one of ordinary skill in the art would have been able to make the presently claimed invention from the teachings of the specification is noted, with appreciation. See, page 4, lines 8-9 of the Office Action dated August 26, 2002 (Paper No. 16). The only outstanding objection appears to be based on the

invention from a teaching of the specification and the generally advanced level of skill in the art. See, page 4, lines 10-11 of Paper No. 16.

Specifically, the Examiner asserts

> "the claimed invention [encompassing uses of the claimed constructs and phagocytes for control of vascularization of developing tissue so as to promote vascularization, or directed to damaged vascular system via an amputation, stroke, cardiac arrest, extreme hypertension, ischemia or burns, and uses of the construct in phagocytes in a tumor under hypoxic conditions to deliver prodrugs or agents having cytotoxic effects to tumor cells in vivo] is not enabled [by the specification] because the specification fails to teach a method of in vivo gene therapy that would overcome the technical difficulties discussed in the prior office action..." See, page 4, lines 11-18 of Paper No. 16.

Elsewhere, the Examiner indicates that because the claims may encompass *in vivo* gene therapy, in humans, human trials of gene therapy are required to demonstrate the "safety and efficacy" of the claimed invention. See, page 5, last paragraph and page 6, first paragraph, of Paper No. 16.

Initially, the applicants note that the specification describes, for example, methods of *in vivo* and *ex vivo* gene delivery/gene transfer. The specification describes methods of gene delivery such as the preparation of a retroviral vector and its transfer to U937 monocytic cell lines (see, page 21, example 1) and gene transfer of primary human macrophages using adenoviral vector (see, Example 2). As exemplified in the specification, efficient transfer of genes into human macrophages has been achieved

transfected monocytes/macrophages have been injected in to diseased tissue of a donor (see, page 38, lines 3-5). Finally, Example 5 demonstrates the effect of clamp induced hypoxia on macrophage infiltration in to tumor xenographs. The clamping of the tumors induces hypoxia in the tumors which leads to increased infiltration of macrophages (see, page 33, lines 23-24). This result demonstrates a correlation between the degree of hypoxia and the number of infiltrating macrophages. Clearly, one of ordinary skill in the art will recognize from these results and the applicants' specification as a whole that mononuclear phagocytes may be used to deliver drugs to hypoxic/ischemic sites where mononuclear phagocytes are typically present (see, page 5, lines 22-25 of the specification).

The applicants submit that the specification is enabling for every aspect of the presently claimed invention. The Examiner is urged to appreciate that if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

Specifically, MPEP § 2164.01(c) states the following:

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana*, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
>
> [illegible] experimentation. It is stated in the art, based on knowledge of compounds having similar physiological or biological

> activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. **The applicant need not demonstrate that the invention is completely safe.** See also MPEP § 2107.01 and § 2107.03. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (claiming a chimeric gene capable of being expressed in any cyanobacterium and thus defining the claimed gene by its use). In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. **In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.** See, MPEP § 2164.01(c) (emphasis added).

The claims are submitted to be supported by an enabling disclosure. The specification teaches one of ordinary skill in the art how to use the claimed invention.

Beyond the above indication that the applicants need not demonstrate that the claimed invention is completely safe, and in response to the Examiner's apparent requirement that the applicants demonstrate that the claimed invention is safe and effective, the applicants submit that the courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or

Specifically, the Federal Circuit, in *Cross v. Iizuka*, 224 USPQ 739, 747-48 (Fed. Cir. 1985), commented on the significance of data from *in vitro* testing that showed pharmacological activity:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility

The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott* [*v. Finney*], 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed.Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The Examiner's apparent requirement for a demonstration of safety and efficacy in

should be withdrawn.

Beyond the specification, the applicants have submitted extensive evidence demonstrating the utility and usefulness of the presently claimed invention.

The applicants respectfully submit that a claimed product needs only one enabled use to satisfy enablement and that an animal model demonstrating that modified mononuclear phagocytes hone to a target site is sufficient to establish one enabled use. Furthermore, such a model is sufficient to extend honing capabilities of claimed cells to *in vivo* scenarios in other hosts irrespective of host response to vector, NOI, etc.

The Examiner is again urged to appreciate that the claimed invention is based upon the discovery that mononuclear phagocytes preferentially congregate in hypoxic (*i.e.* poorly vascularised and necrotic) sites deep within a tumor mass remote from blood vessels. The specification and evidence of record support claims based on the discovery that mononuclear phagocytes modified to express a gene of interest in operable linkage with an hypoxic, ischemic or regulatable element possess this ability to hone to the target site, *i.e.*, tumor cell.

The comments of the Examiner relating to nude mice, *e.g.*, host immune responses, are, with due respect, believed to be irrelevant to the claimed invention as the claims directed to such modified mononuclear phagocytes are fully enabled by the *in vivo* model supporting that these cells target hypoxic sites within the implanted human tumors.

The Examiner's comments on page 6 of Paper No. 16 relating to an apparent requirement for human trials have been addressed above. The nude mouse evidence of

See page 5 of Paper No. 16. Successful results demonstrated with a "standard" procedure

model" must be predictive of how to use the subject of the demonstration. The applicants submit the evidence of the Declaration is further compelling evidence that one of ordinary skill in the art would have been able to use the claimed invention given the teachings of the specification and the generally advanced level of skill in the art.

Moreover, the Examiner has not offered any evidence in support of the assertions that the specification fails to teach one of ordinary skill how to use the claimed invention, beyond concerns about host immune systems and safety and efficacy in human trials. The applicants believe that properly reasoned and supported statements explaining any failure to comply with Section 112, first paragraph, are a requirement to support a rejection and in the absence of the same, the rejection should be withdrawn.

Withdrawal of the Section 112, first paragraph, "how to use" rejection of the claims and a Notice of Allowance are requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Amend the claim as follows.

Cancel claims 94, 102, 103, 105-108, 117-119 and 126, without prejudice.

88. (Amended) The mononuclear phagocyte according to claim 87 wherein expression of the NOI is regulated by the regulatable element at a target [hypoxia and/or ischemic and/or stress site] site selected from the group consisting of an hypoxic site, an ischemic site, a stress site, and a site being a combination of at least two of an hypoxic site, an ischemic site, and a stress site.

90. (Amended) The mononuclear phagocyte according to claim 89 wherein the binding agent comprises [a ligand adapted to bind to the cell surface element of the mononuclear phagocyte, preferably wherein the ligand is] a mannosylated poly – L – lysine ligand.

101. (Amended) The mononuclear phagocyte according to claim 87 wherein the mononuclear phagocyte further comprises an NOI encoding HIF1-alpha [an activating] or [control product] a tetracycline repressor protein.

according to claim 87 to a target [hypoxic and/or ischemic and/or stress] site selected

from the group consisting of an hypoxic site, an ischemic site, a stress site, and a site being a combination of at least two of an hypoxic site, an ischemic site, and a stress site.

110. (Amended) The mononuclear phagocyte according to claim 87 wherein the hypoxia[c], [and/or] ischemic [and/]or stress [associated condition] is a tumour associated condition.

121. (Amended) A pharmaceutical composition comprising a construct according to claim [87] 111 optionally admixed with a pharmaceutically acceptable diluent, excipient or carrier.